Remarks and Arguments

Claims 1-15, 23 and 25-34 were rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,700,642 ("Monforte '642"). This rejection is repeated from the examiner's last office action. In the applicants' last response, the Monforte '642 reference was discussed at length. Therein, it was argued that the Monforte '642 differed significantly from the present invention. In an embodiment highlighted by the examiner, in which Monforte '642 uses a chip to which primers are attached, the reference discloses a "shotgun" type method of sequence analysis in which different primers are immobilized at different locations on a sample support. However, this method is limited to the situation in which there is one target sequence being sequenced. It is not used for mutation analysis of a plurality of target sequences. This is in contrast to the present invention, which uses a chip with spatially separated locations each containing a photocleavable probe for a *different* one of a number of different target sequences to be investigated. Independent Claim 1 was amended in the last response to make this distinction even more apparent, by specifying the use of "a chip with spatially separated locations each containing a photocleavable oligonucleotide probe for a different one of the target sequences to be investigated."

In response to this argument made by the applicant, the examiner now points to a different section of the Monforte '642 reference as teaching the use of a set of different primers. In particular, the examiner cites column 26, lines 1-12, which reads:

> [a]lternatively, instead of selecting a conserved region adjacent a hypervariable region, a series of unique primers can be created that will hybridize to a hypervariable or unique region of a selected pathogen. Enzymatic extension of these primers provides sequence information about an adjacent segment of the hypervariable region. This methodology enables specific identification of each pathogen sequence present in a mixed population. Utilizing this approach, one may target different hypervariable regions for each target pathogen. This approach may be preferred for identifying viruses for which there is often very little conservation among other viruses or bacteria.

As stated in this section, the objective of this technique by Monforte '642 is to identify pathogens or microorganisms. However, this technique is different than the shotgun

sequencing technique of Monforte '642 in which primers are immobilized on a sample support. Indeed, while Monforte '642 discloses the use of an immobilization surface, such as a chip, for the sequencing of one target sequence, there is no suggestion of doing so for mutation analysis of a plurality of target sequences. However, in the multiplexed analysis method of the present invention, a chip to which probes are attached at spatially separated locations is an integral part of the invention. Monforte '642 provides no suggestion of a multiplexed method in which primers are immobilized on a chip.

The examiner has also commented that there is no claim limitation that addresses the point that the present invention permits sequential analysis at separate locations on the chip. To clarify this point, Claim 1 has been amended to specify "cleaving and mass spectrometrically measuring the probes *one after another*." The argument made by the examiner that Claim 6 contradicts this aspect of the invention appears to have resulted from a misunderstanding of the language of that claim. Claim 6, as examined, stated that "the photolytic cleavage of the oligonucleotide probes from the solid substrate surface occurs simultaneously with their desorption and ionization in the laser desorption pulse." That is, the cleavage of each probe occurred at the same time as the desorption and ionization, not at the same time as all the other probes. However, to clarify this language, Claim 6 has been amended to state that "the photolytic cleavage of *each of* the oligonucleotide probes from the solid substrate surface occurs simultaneously with *its* desorption and ionization in the laser desorption pulse." As such, it should now be clear that there is no inconsistency with the language of Claim 6 and that of Claim 1.

As amended, Claim 1 is clearly unsuggested by Monforte '642, which fails to suggest a method of mutation analysis of a plurality of target sequences that uses a plurality of different probes covalently bound to spatially separated locations on a chip, modifies all oligonucleotide probes on the chip synchronously to transfer information from the target sequences of the templates to the probes, and cleaves and mass spectrometrically measures the probes one after another after separating them from the

templates. Each of Claims 2-15, 23 and 25-34 depends ultimately from Claim 1 and is therefore equally unsuggested by the cited prior art. Reconsideration of Claims 1-15, 23 and 25-34 under this ground for rejection is respectfully requested.

Claims 1-19, 23 and 25-34 were rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,830,655 ("Monforte '655"). The Monforte '655 reference was discussed in a prior response filed by the applicants, and that earlier discussion is incorporated here. Although the examiner notes that the two Monforte patents are not identical, they are quite similar in subject matter, one being a continuation-in-part of the other. Indeed, for the purposes of the broadest of the claims rejected hereunder, the application of Monforte '655 appears to parallel that of Monfore '642. As such, all of the arguments made above with regard to the allowability of Claim 1 in light of Monforte '642 are believed to apply to this rejection as well. Monforte '655 fails to suggest a method of mutation analysis of a plurality of target sequences that uses a plurality of different probes covalently bound to spatially separated locations on a chip, modifies all oligonucleotide probes on the chip synchronously to transfer information from the target sequences of the templates to the probes, and cleaves and mass spectrometrically measures the probes one after another after separating them from the templates. Each of Claims 2-19, 23 and 25-34 depends ultimately from Claim 1 and is therefore equally unsuggested by the cited prior art. Reconsideration of Claims 1-15, 23 and 25-34 under this ground for rejection is respectfully requested.

Claims 1-34 were rejected under 35 U.S.C. §103(a) as being obvious over Monforte '655 in view of U.S. Patent No. 6,251,600 ("Winger"). This rejection was also repeated from the last office action, and the references cited were discussed in the applicants' last response. Those comments are incorporated herein. In that last response, the applicants also questioned the need to apply this prior art combination to all of Claims 1-34, since most of those claims were already rejected under Monforte '655 alone. The examiner apparently disagrees with the applicants' assessment in this regard, citing case law to support the proposition that "anticipation is the ultimate of obviousness." The applicants certainly do not dispute this basic premise, but note that

the examiner indicated that Claims 20-22 and 24 were the only claims for which the Winger reference was required under this rejection. It therefore appears that, for each of Claims 1-19, 23 and 25-34, Winger is completely superfluous.

The examiner's rejection based on Monforte '655 and Winger appears to rely exclusively on Monforte '655 as suggesting all of the limitations of independent Claim 1. However, as discussed above, there are some significant differences between this prior art reference and Claim 1 as amended. These differences persist when it is taken in combination with Winger. There is nothing in the combination of Monforte '655 and Winger that suggests a method of mutation analysis of a plurality of target sequences that uses a plurality of different probes covalently bound to spatially separated locations on a chip, modifies all oligonucleotide probes on the chip synchronously to transfer from the target sequences of the template to the probes, and cleaves and mass spectrometrically measures the probes one after another after separating them from the templates. Each of Claims 2-34 depends ultimately from Claim 1 and is therefore equally unsuggested by the cited prior art. Reconsideration of Claims 1-34 under this ground for rejection is respectfully requested.

In light of the foregoing amendments and remarks, all of the claims of the application are believed to be in condition for allowance, and such allowance is hereby respectfully requested. If it is believed that a telephone conference would help expedite prosecution of the application, the examiner is invited to call the undersigned. The Commissioner is hereby authorized to charge any fees due for the filing of this paper to the applicants' attorneys' Deposit Account No. 02-3038.

Respectfully submitted

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